

What exactly is myalgic encephalomyelitis?

Although there are good diagnostic criteria for myalgic encephalomyelitis, knowledge of the disease is often lacking and this can result in misdiagnosis and incorrect treatment. There is a need for more research, greater expertise among clinicians, and refinement of the diagnostic criteria.

Torstein Egeland
torstein.egeland@medisin.uio.no
Arild Angelsen
Ruth Haug
Jan-Olav Henriksen
Tor Erling Lea
Ola Didrik Saugstad

In the literature and in clinical practice, «chronic fatigue syndrome» (CFS) and myalgic encephalomyelitis (ME) are sometimes used synonymously (1). Limited knowledge of aetiology and pathology has resulted in a variety of terms being used to refer to various long-term pain and fatigue disorders of unknown origin. Research over recent years, the establishment of good diagnostic criteria, and clinical experience, however, indicate that myalgic encephalomyelitis is a reasonably well-defined disorder with distinct clinical characteristics.

Jason and colleagues have highlighted the fact that patients with myalgic encephalomyelitis have more severe symptomatology than those with chronic fatigue syndrome, but better mental health (2). In common with Jason, one of the leading researchers in the field internationally, we believe that it is important to distinguish between myalgic encephalomyelitis and chronic fatigue syndrome (2, 3). Myalgic encephalomyelitis should be considered a distinct diagnostic category, not least because post-exertional malaise, significant functional impairment and sleep disturbances are cardinal symptoms.

Advances in research and increasing clinical experience are reflected in the evolution of the various diagnostic criteria into the current international consensus criteria for myalgic encephalomyelitis (4) and the most recent proposal from the Institute of Medicine in the USA (5). Box 1 presents an overview of the various criteria that have been in use over the past 25 years, from the broadest Oxford criteria (general fatigue) to criteria with a focus on specific symptoms of myalgic encephalomyelitis: the Canadian criteria (6) and the international consensus criteria for myalgic encephalomyelitis (4).

The use of different diagnostic criteria

makes it difficult to establish the prevalence of myalgic encephalomyelitis specifically. Depending on which criteria are used, the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis is probably around 0.1–2.5%. The incidence per 100 000 population in Norway is estimated at 39.4 (women) and 12.9 (men) (7), with slight peaks at the ages of 10–19 and 35–49 years (7).

Many studies have included very heterogeneous patient populations, where perhaps only a minority of individuals had what we would define as myalgic encephalomyelitis. As a result, it has been difficult to unambiguously identify aetiological and pathogenic factors in the disease. Several studies do, however, indicate that the condition has a somatic origin. Changes in the central nervous system and the immune system have been described, as well as dysfunction of cellular energy metabolism and ion transport, cardiovascular changes, endocrine hypoactivity and a possible genetic predisposition (4, 8). Development of myalgic encephalomyelitis after infection or vaccination is well known and may indicate a post-infectious origin (8, 9). A recent Norwegian study showed that antibody treatment against B lymphocytes had beneficial effects in a majority of patients (10), a new PET study from Japan shows widespread inflammation of the central nervous system (11), and Brown and colleagues recently demonstrated abnormal activation of AMPK and glucose uptake in skeletal muscle (12). Two recently published articles show a series of changes in immunological variables in plasma in patients ≤ 3 years after onset of myalgic encephalomyelitis/chronic fatigue syndrome (13) and in cerebrospinal fluid in a patient cohort (14).

How is the diagnosis made?

Myalgic encephalomyelitis is diagnosed via a careful anamnesis and thorough physical examination. Other conditions must be excluded, and there are currently no diagnostic biomarkers. The Norwegian Directorate of Health's guidelines (1) recommend either the Fukuda- or Canadian criteria for adult patients, see Box 1. This

might appear confusing given that the criteria are incongruent. The guidelines also emphasise that «prolonged worsening of fatigue after physical or mental exertion is considered a cardinal symptom», even though this is an absolute requirement only in the Canadian criteria and the international consensus criteria for myalgic encephalomyelitis. The frequency and intensity of symptoms are also important for distinguishing patients with myalgic encephalomyelitis from other groups with chronic fatigue symptoms (2).

The use of broad inclusion criteria has created a heterogeneous patient population, also within research. This has increased the risk of erroneous conclusions, misdiagnosis and incorrect treatment (15). For myalgic encephalomyelitis, the Canadian criteria and the international consensus criteria have in our view increased the accuracy of diagnosis due to their greater specificity and clearer delineation of the disorder from other forms of fatigue.

The Norwegian Directorate of Health recommends that children and adolescents are diagnosed by a paediatrician. Adults can be diagnosed by their general practitioner (1). Given how unclear this field has been previously, and how time-consuming an assessment can be, we believe it is very important that doctors who make the diagnosis have broad experience and extensive knowledge of the condition and of diseases with overlapping symptoms.

How are patients treated?

The assessment and treatment of patients with myalgic encephalomyelitis and chronic fatigue syndrome/myalgic encephalomyelitis in Norway is, according to a SINTEF study from 2011 (16), highly inadequate: There is a lack of expertise within the social, welfare and healthcare services, and disagreement over the diagnostic criteria. Furthermore, the provision of appropriate treatment, rehabilitation and care is lacking, as is expertise regarding the particular needs of children and adolescents. Research activity is limited. Patients experience stigma and a lack of respect from healthcare personnel.

There is no specific treatment. We believe that myalgic encephalomyelitis may consist of several subtypes, which cannot at present be distinguished using existing diagnostic criteria. Such subtypes may have distinct aetiologies and pathogenic mechanisms, which could require different therapeutic approaches.

Internationally, myalgic encephalomyelitis has gradually come to be viewed as a somatic disorder, partly as a result of new and better research. In the USA, this view is gaining ever-increasing support and is now dominant within leading research communities (4, 8–14). However, as a result of the previously more psychosomatic view of the disease, and also the broad diagnostic criteria, various psychological and psychosomatic approaches have been used in an attempt to treat patients. The idea was that shifting the psyche towards positive thinking using techniques such as cognitive behavioural therapy (CBT) and/or various forms of graded exercise therapy (GET) would give good clinical results. Some patients have benefited from such treatment, and cognitive behavioural therapy can improve patients' ability to cope with the disease. However, others have experienced no effect or have even deteriorated (17–19). Health professionals must therefore keep in mind that treatments requiring physical or mental exertion can often lead to patients becoming overstrained and to worsening of symptoms. We refer again to the statement in the national guidelines regarding prolonged deterioration following physical or mental exertion (1).

Treatments such as cognitive behavioural therapy and graded exercise therapy are controversial in the literature, with some studies reporting improvement of symptoms and others reporting exacerbation. However, it is difficult to draw conclusions from many of these clinical studies given that patient populations were often heterogeneous and limited, differing diagnostic criteria were used and methods of assessment and follow-up varied.

A report recently submitted to the US health authorities concludes that continued use of the Oxford criteria (the broadest) «may impair progress and cause harm», and recommends that these criteria should no longer be used (20). Nevertheless, studies based on these broad criteria are still used to recommend specific treatments; see for example the Norwegian Knowledge Centre for the Health Services' article on how exercise therapy can help persons with chronic fatigue syndrome/myalgic encephalomyelitis (21).

However, the results of large user surveys conducted by patient associations in

BOX 1

Various diagnostic systems and criteria for myalgic encephalomyelitis, chronic fatigue syndrome and chronic fatigue syndrome/myalgic encephalomyelitis are used in clinical diagnostics and research. The most common are:

Oxford criteria for chronic fatigue syndrome (1991)

Drafted by an English group consisting largely of psychiatrists (27). The main criterion is severe fatigue for at least six months. Other diseases must be excluded. The Oxford criteria are very broad, but are still used to some degree in research. Neither the Norwegian Directorate of Health nor the US health authorities recommend use of these criteria today.

Fukuda criteria for chronic fatigue syndrome (1994)

Drafted by the Centers for Disease Control and Prevention (CDC) on the basis of Fukuda et al. (28). In addition to severe fatigue for at least six months, and the exclusion of other diseases, at least four of eight defined symptoms must be present: impaired short-term memory and/or concentration, sore throat, tender lymph nodes, muscle pain, joint pain, new-onset headache, unrefreshing sleep, and post-exertional malaise. These criteria have been central to research.

Canadian criteria for myalgic encephalomyelitis/chronic fatigue syndrome (2003)

Drafted by doctors and researchers and represent a refinement and narrowing of the Fukuda criteria (6). The Canadian criteria require the patient to have six different symptoms: severe physical and mental fatigue, post-exertional malaise or fatigue, sleep dysfunction, pain in muscles, joints and the head, neurological/cognitive features (minimum of two symptoms, e.g. confusion, impaired concentration, ataxia), and autonomic, e.g. nausea and irritable bowel, neuroendocrine, e.g. loss of thermostatic stability, or immune disorders.

International consensus criteria for myalgic encephalomyelitis (2011)

Drafted by an international panel of experts from 13 countries (4) and a refinement of the Canadian criteria. A diagnosis of myalgic encephalomyelitis requires the patient to fulfil criteria within four categories: (a) post-exertional neuroimmune exhaustion, often with significantly prolonged recovery period, (b) neurological impairments, i.e. symptoms from three of four categories: cognitive abilities, pain, sleep disturbances and/or neurosensory, perceptual or motor disturbances, (c) immune, gastrointestinal and genitourinary impairments from three of five categories, including flu-like symptoms, nausea and hypersensitivity, and (d) impairments of energy production and energy transport within one of four categories: cardiovascular, respiratory, thermoregulatory and/or intolerance of extreme temperatures. The criteria have also been adapted for paediatric populations.

Paediatric criteria for myalgic encephalomyelitis and chronic fatigue syndrome (2006)

Various paediatric diagnostic criteria have been used. The Norwegian Directorate of Health recommends the criteria presented by Jason *et al.* (29), which require chronic fatigue for at least three months and exclusion of other diseases. Additional requirements include post-exertional malaise/fatigue, unrefreshing sleep or other sleep disturbances, pain in muscles, joints, stomach or head, neurocognitive features, at least 2 of 12, and at least one symptom within the three groups autonomic, neuroendocrine and immune. Severe psychiatric disorders that could explain the chronic fatigue, such as anorexia and bulimia, are exclusionary.

«Systemic Exertion Intolerance Disease» (SEID) criteria (2015)

Proposed by the Institute of Medicine in the United States (5). The diagnosis requires a significant loss of functional capacity, post-exertional malaise (PEM) and sleep disturbances (unrefreshing sleep). Additional criteria are also proposed, including cognitive impairment and/or orthostatic intolerance. The proposers suggest that the term myalgic encephalomyelitis should be replaced with «Systemic Exertion Intolerance Disease» (SEID).

Norway (17) and the UK (18) are more clear-cut and surprisingly similar: Cognitive behavioural therapy had little or no effect in most, while a minority experienced either improvement or deterioration. For graded exercise therapy the results are discouraging: 66 % of patients surveyed in Norway and 56 % in the UK became worse, sometimes markedly so. Only 14 % of patients in Norway and 22 % in the UK experienced an improvement. Approximately seven out of ten patients in both studies found that pacing led to an improvement in their condition. The Cochrane and PACE studies (22, 23) are often used as grounds for recommending cognitive behavioural therapy for myalgic encephalomyelitis, but even these two studies show that cognitive behavioural therapy is helpful in only a minority of patients when compared to a control group and standard monitoring by a doctor.

We therefore feel it is unfortunate that psychosomatic therapy continues to be recommended by the health authorities and in parts of the healthcare system (21, 24–26). We recognise that it is difficult to distinguish those patients who may benefit from psychosomatic therapy from those who should receive a different form of treatment. This should lead to increased consideration of patients as individuals and greater care regarding choice of therapy. Patients' experiences and knowledge of their own limitations should be taken seriously, and it may also be helpful to involve relatives.

We are aware of far too many cases of patients with severe myalgic encephalomyelitis being poorly received by doctors and other healthcare professionals. The status of patients in Norway poses serious ethical challenges for the Norwegian healthcare system. Many of those affected report that they are given unhelpful or even harmful treatment (17, 18). Greater expertise regarding how to diagnose the disorder, which forms of treatment are most appropriate, and how the disease manifests for the patient and their close family would be highly useful for both clinicians and patients. In particular, we believe that classic symptoms such as cognitive impairment and activity intolerance (post-exertional malaise) must form the basis of both diagnosis and treatment, as in the new criteria proposed by the Institute of Medicine (5), and not be misinterpreted as an unwillingness on the part of the patient to acknowledge or improve their own situation (17, 18).

A more deliberate use of the diagnostic criteria will result in increased understanding of the disease and of patients' lives, and more respectful and appropriate treatment. It will also lay the foundations for

ramping up (5, 20) biomedical research efforts in the hope of developing more effective treatments.

We are six professors who, in different ways, are all involved in issues related to myalgic encephalomyelitis. Some of us are medics and scientists who participate actively in research into the condition, while others are social scientists or ethicists who have taken a critical look at the literature in the field from a social and socio-medical perspective.

Torstein Egeland (born 1951)

adjunct professor in the Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, and head of the Section of Transplantation Immunology, Department of Immunology, Oslo University Hospital.

The author has completed the ICMJE form and reports no conflicts of interest.

Arild Angelsen (born 1961)

professor of economics at the School of Economics and Business, Norwegian University of Life Sciences.

The author has completed the ICMJE form and reports no conflicts of interest.

Ruth Haug (born 1957)

professor of development studies in the Department of International Environment and Development Studies, Faculty of Social Sciences, Norwegian University of Life Sciences.

The author has completed the ICMJE form and reports no conflicts of interest.

Jan-Olav Henriksen (born 1961)

Dean of Research and professor of systematic theology, Norwegian School of Theology (MF), Oslo, and professor of contemporary religion at the University of Agder.

The author has completed the ICMJE form and reports no conflicts of interest.

Tor Erling Lea (born 1947)

professor of immunology, food and health in the Department of Chemistry, Biotechnology and Food Science, Faculty of Veterinary Medicine and Biosciences, Norwegian University of Life Sciences.

The author has completed the ICMJE form and reports no conflicts of interest.

Ola Didrik Saugstad (born 1947)

professor of paediatric medicine at the University of Oslo, head of the Department of Women's and Children's Health, Oslo University Hospital, and director of the Department of Paediatric Research, University of Oslo and Oslo University Hospital.

The author has completed the ICMJE form and reports no conflicts of interest.

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